PATENT SPECIFICATION

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(54) PHARMACEUTICAL COMPOSITIONS AND THEIR PREPARATION

(71) We, GIST-BROCADES N.V., a Dutch Body Corporate of Wateringsweg 1, Delft, Holland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pharmaceutical compositions and to their preparation.

Liquid compositions prepared from bismuth salts, such as bismuth citrate or bismuth subnitrate, are known. Such liquid preparations have the disadvantage that they are less easy to store and to transport than solid compositions. The fact that they are only stable within a limited pH-range and when they contain ammonia and that the pH can become too low by loss of ammonia, constitutes another disadvantage of such preparations. They cannot easily be converted into an effective solid product, e.g. by simply heating and drying.

According to the present invention a solid bismuth-containing powder is prepared by spray-drying an aqueous, colloidal solution comprising bismuth citrate, ammonia and a non-toxic polyhydric alcohol to produce a dry powder. This powder is useful for making pharmaceutical compositions in unit dosage form for oral administration. The liquid starting material optionally contains pepsin, a colouring agent such as carmine, an alkali metal (e.g. sodium or potassium) hydroxide and a preservative, such as the mixture of water-soluble salts of esters of *p*-hydroxybenzoic acid, sold under trade name Nipacombin A.

Known liquid preparations containing bismuth sometimes contain volatile liquids, such as ethanol or chloroform. Such liquids may be present in the starting material used in the process of the invention in an amount not exceeding 15% (v/v), but they have virtually no effect on the process or on the product obtained. Generally speaking, the commercially available liquid preparations comprising bismuth citrate, ammonia and a polyhydric alcohol, may be used to carry out the process of the invention. It is not certain whether the bismuth citrate, ammonia and polyhydric alcohol are present as such in the liquid or whether they form a new molecule or ion.

The bismuth citrate may be used as such or it can be formed *in situ*, e.g. from citric acid and a bismuth salt with a physiologically acceptable anion. The liquid is most stable at a pH approximately 9. When the pH is considerably lower or higher a precipitate is formed. Especially when the liquid has to be stored for some time before spray-drying, it is therefore recommended to use enough ammonia and alkali metal hydroxide to produce this pH. The amount of ammonia should at least be sufficient to keep the bismuth in solution.

Preferred polyhydric alcohols are disaccharides such as sucrose or maltose, and the use of poisonous such alcohols, e.g. ethylene glycol must, of course, be avoided.

The dry powder of the invention can be produced from the liquid in a conventional spray-drying unit. The liquid starting material may for example contain from 1% to 16%(w/v) of solids. The solution is preferably preheated at a temperature of 60 to 65°C. The heating time should be such that no undesired reaction takes place. For instance, when sucrose is used, the heating time should not exceed 20 minutes in order to prevent inversion. The solid product resulting from the process of the invention is very hygroscopic. It is therefore recommended to remove the moisture from the spray-drying unit by preheating, for instance for 30 minutes with an inlet air temperature of about 200°C. During the drying process the inlet air temperature is preferably from 150 to 220°C, a temperature from 170 to 190°C being particularly preferred, and the outlet temperature is preferably from 50 to 110°C. The liquid should be fed to the unit at such a speed that the evaporative capacity of the drier is sufficient to form a dry powder.

The solid product obtained by this

process can be administered orally as such or it may be dissolved in water to produce a palatable solution.

The invention includes within its scope pharmaceutical compositions in unit dosage form for oral administration, such as capsules or tablets, containing the therapeutically active dry bismuth preparation of the invention as the active ingredient. The compositions may also contain pharmaceutically-acceptable carriers.

Tablets may be formulated in the usual manner with one or more pharmaceutically-acceptable diluents or excipients, for example lactose or starch, and include materials of a lubricating nature, for example calcium stearate or magnesium stearate. Capsules made of absorbable materials, such as gelatin, may contain the active substance alone or in admixture with a solid or liquid diluent.

The compositions of the invention are therapeutically effective in the treatment of peptic ulcer, including gastric, duodenal and post-operative ulcer and peptic ulcer associated with hiatus hernia. Suitable daily dosages for adult humans correspond to 450—1000 mg of Bi_2O_3. The dosage for children depends on their weight and age and may be calculated by methods commonly used in medical practice. The daily dose for children under 10 years is 150—400 mg of Bi_2O_3. The pharmaceutical compositions in dosage form therefore preferably have a bismuth content equivalent to 50—250 mg of Bi_2O_3 per dosage unit.

The following Example illustrates the process of the invention.

Example I

1,500 litre of liquid is prepared by mixing:

180.360 kg of bismuth citrate
118.279 l of ammonia 25% (w/v)
7.125 kg of pepsin 1:10.000
23.700 kg of anhydrous citric acid
0.990 l of carmine nacarat
8.051 l of glycerol
330.000 kg of sucrose
39.900 kg of potassium hydroxide
3.000 kg of Nipacombin A 0.2% (w/v)
8.700 l of chloroform
94.050 l of ethanol

and purified water, to produce the desired volume.

The solution obtained is diluted with water to a solids-content of 12% (w/v) and the diluted liquid is preheated at 60—65°C for 15 minutes. A spray-drying unit with an evaporative capacity of 10 kgs/h is preheated for 30 minutes with an inlet-air temperature of 200°C. The liquid is subsequently fed to the atomizer with a speed of 9 litres per hour, the inlet-air temperature being maintained at 180°C, and the dry powder formed is collected.

The following Example illustrates a pharmaceutical composition according to the invention.

Example II

Using known pharmaceutical techniques, tablets are prepared, containing 450 mg of the spray-dried product prepared according to Example I, 25 mg of Aerosil 200 (purified silicon dioxide), 50 mg of corn starch, and 5 mg of magnesium stearate. (Aerosil is a Registered Trade Mark)

The invention includes within its scope the preparation of an aqueous solution from the dry powder. For instance, a solution suitable for oral administration may be obtained by dissolving 200 g of the powder prepared according to Example I in water to a volume of 1 litre. Other physiologically-acceptable substances may be added, for instance to produce a desired pH or to improve the taste of the solution.

WHAT WE CLAIM IS:—

1. A process for the preparation of a solid bismuth-containing powder which comprises spray-drying an aqueous, colloidal solution comprising bismuth citrate, ammonia and a non-toxic polyhydric alcohol, to produce a dry powder.

2. A process according to claim 1 in which the said colloidal solution contains from 11 to 16% (w/v) of solids.

3. A process according to claim 1 or 2 in which the said colloidal solution is preheated at 60—65°C before spray-drying.

4. A process according to claim 1, 2 or 3 in which the spray-drying unit is preheated to remove moisture therefrom.

5. A process according to claim 4 in which the spray-drying unit is preheated with an air inlet temperature of 200°C.

6. A process according to any of claims 1 to 5 in which the inlet air temperature in the spray-drying unit is from 150 to 220°C during the spray-drying operation.

7. A process according to claim 6 in which the inlet air temperature is from 170 to 190°C.

8. A process according to claim 1 substantially as described in Example I.

9. A dry powder obtained by the process claimed in any of claims 1 to 8.

10. A pharmaceutical composition in unit dosage form for oral administration, comprising a dry powder according to claim 9.

11. A pharmaceutical composition

according to claim 10 having a bismuth content equivalent to 50—250 mg of Bi_2O_3 per dosage unit.

12. A process for the preparation of a bismuth-containing liquid for oral administration, which comprises dissolving a dry powder as claimed in claim 9, in water.

13. A composition according to claim 10 substantially as described in Example II.

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